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California Institute for Regenerative Medicine

Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells.

Grant Award Details

Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells.

Grant Type: SEED Grant

Grant Number: RS1-00171

Investigator:

Name: Huei-sheng Chen

Institution: Sanford-Burnham Medical Research Institute

Type: PI

Disease Focus: Heart Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $695,680

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells.

Public Abstract:

Optimal cardiac function depends on the properly coordinated cardiac conduction system (CCS). The CCS is a group of specialized cells responsible for generating cardiac rhythm and conducting these signals efficiently to working myocardium. This specialized CCS includes the sinoatrial node, atrioventricular node and His-Purkinje system. These specialized pacemaking /conducting cells have different properties from the surrounding myocytes responsible for the contractile force. Genetic defects or postnatal damage by diseases or aging processes of these cells would result in impaired pulse generation (sinus node dysfunction, SND) or propagation (heart block). Implantation of an electronic cardiac pacemaker is necessary for intolerant bradycardia to restore cardiac rhythm. However, the electronic implantable pacemaker has multiple associated risks (e.g. infections) and requires frequent generator changes due to limited battery life. Sinus node dysfunction is a generalized abnormality of cardiac impulse formation and accounts for >30 percent of permanent pacemaker placements in the US. A perfect therapy to SND will be to repair or replace the defective sinus node by cellular or genetic approaches. Many recent studies have demonstrated, in a proof-of-concept style, of generating a biological pacemaker by implanting various types of progenitor or stem cells into ventricular myocardium to form a pulse-generating focus. However, a perfect biological pacemaker will require good connections with the intrinsic neuronal network for proper physiological responses. Elucidation of the factors controlling the evolution of pacemaker cells and their interaction with the peripheral neuronal precursor cells (neural crest cells, NCCs) will be paramount for creating an adaptive biological pacemaker. The NCCs have been shown to be contiguous with the developing conduction system in embryonic hearts of humans. However, the influence and interaction of the NCCs with the developing cardiac pacemaker cells remains unclear. In addition, there is no simple marker for identifying the pacemaker cells and the electrophysiological (EP) recording is the only physiological method to trace the evolution of cardiac pacemaker cells from human embryonic stem cells (hESCs). We have successfully obtained the EP properties of early hESC-derived cardiomyocytes. We propose here an in vitro co-culture system to study fate of the pacemaker cells evolved from hESCs and to investigate the influence of NCCs on the early, cardiac committed myocytes derived from hESCs. Such a study will provide insight in the development of pacemaker cells and in the mechanisms of early neuro-cardiac interaction. Results from the proposed study may suggest strategies for developing efficient and neuro-coupled cardiac pacemakers from ESCs. These neuro-coupled biological pacemaker cells may one day used clinically to replace the need for implanting an electronic pacemaker for the treatment of intolerant bradycardia.

Statement of Benefit to California:	Optimal cardiac function depends on the properly coordinated cardiac conduction system. Genetic defects or postnatal damage by diseases or aging processes of these pacemaker cells would result in impaired pulse generation (sinus node dysfunction) or propagation (heart block). The implantation of an electronic cardiac pacemaker is necessary for intolerant bradycardia to restore physiologic cardiac rhythm. However, the electronic implantable pacemaker has multiple associated risks (e.g. infections and thrombosis) and requires frequent generator changes due to limited battery life. Sinus node dysfunction (SND) is a generalized abnormality of cardiac impulse formation and accounts for 30-50 percent of permanent pacemaker placements in the US. A perfect therapy to SND will be to repair or replace the defective sinus node by cellular or genetic approaches. Most of the research work on developing biological pacemakers are performed in Columbia University at New York City, Johns Hopkins University at Baltimore, and Technion-Israel Institute of Technology at Haifa, Israel. All of their approaches produced short-lived and non-responsive biological pacemakers to physiological demands. None of human stem cell-related research in California is devoted to this highly promising field of developing biological pacemakers. The proposed research here will elucidate the factors controlling the evolution of pacemaker cells and their interaction with the peripheral neuronal precursor cells (neural crest cells). Such a study will provide insight in the development of pacemaker cells and in the mechanisms of early neuro-cardiac interaction. These factors then can be used to generate better neuro-coupled biological pacemaker cells in California. These neuro-coupled biological pacemaker cells may one day be used clinically to replace the need for implanting an electronic pacemaker for the treatment of intolerant bradycardia. Creating the neuro-coupled, adaptive biological pacemakers will make California the epicenter of the next generation of pacemaker therapy, and will benefit its citizens who have intolerant cardiac bradycardia.